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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/663,506	09/15/2003	Muhammad Ashraf	AM-101106US	1850

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EXAMINER	
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ART UNIT	**PAPER NUMBER**
1617	

DATE MAILED: 05/04/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/663,506	ASHRAF ET AL.	
	Examiner	Art Unit	
	Kendra D. Carter	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-6 and 9-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-6 and 9-19* is/are rejected.

7)☒ Claim(s) *1-6 and 9-19* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/4/03, 3/31/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 1-6 and 9-19, are drawn to a pharmaceutical composition for oral administration comprising a granulation of CCI-779, a water soluble polymer, a surfactant, an antioxidant, and a pH modifying agent, classified in class 514, subclass 659 and class 546, subclass 282.7.

II. Claims 7-8, are drawn to a process for preparing a CCI-779 oral composition, classified in class 514, subclass 659 and class 546, subclass 282.7.

The inventions are distinct, each from the other because of the following reasons:

Inventions of Group I and Group II are related as process of making and product made. The inventions are distinct if either or both of the following can be shown: (1) that the process as claimed can be used to make other and materially different product or (2) that the product as claimed can be made by another and materially different process (MPEP § 806.05(f)). In the instant case, the invention of Group I can be prepared by different processes. In addition the process of Group II can be used to prepare different compositions.

Because these inventions are distinct for the reasons given above and the search required for Group I is not required for Group II, restriction for examination purposes as indicated is proper. It is noted that while the searches of Groups I and II

may be overlapping, there is no reason to believe that the searches would be coextensive. In searching Group I, Examiner will be focusing on the patentability of a composition comprising CCI-779, and not the process by which it was prepared. Conversely, in searching Group II, Examiner will be focusing on the patentability of the process of preparing a composition of CCI-779 and not the composition itself.

During a telephone conversation with Cathy Kodroff on April 7, 2006 a provisional election was made with traverse to prosecute the invention of Group I, claims 1-6 and 9-19. Affirmation of this election must be made by applicant in replying to this Office action. Claims 7-8 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Title

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. The Examiner suggests adding the active compound 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid to the title because oral formulations is very vague. Therefore the title would read, "Oral formulations of 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid".

Claim Objection

Claims 1-6 and 9-19 objected to because of the following informalities: The compound "CCI-779" should include the proper name 3-hydroxy-2-(hydroxymethyl)-2-methylpropionic acid. Appropriate correction is required.

***Claim Rejections* – 35 USC § 102**

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-6, 9-12 and 15-17 are rejected under 35 U.S.C. 102(e) as being anticipated by Zhu el. al. (US 2002/0055518 A1).

Zhu et. al. teaches a pegylated hydroxyester of rapamycin which are useful for inducing immunosuppression (see abstract). A pharmaceutical composition which comprises a compound having the structure shown on page one, paragraph 8 wherein R^1 is $-CO(CR^3R^4)_b(CR^5R^6)_dCR^7R^8R^9$; b=0, d=1, R^5 and R^6 are each $-(CR^3R^4)_fOR^{10}$, wherein R^3, R^4 R^{10}, and R are each hydrogen and f=2 (see page 10, column two, claim 16, for example), which is the same compound that the applicant discloses as CCI-779 in claims1-6 and 9-19. Oral formulations containing the active compound of this invention may be made by wet or dry granulation, (disclosed in applicants claims 1-6 and 9-19 as a granulation) method and utilize pharmaceutically acceptable diluents, binding agents, lubricants, disintegrants, surfactants, suspending or stabilizing agents, including but not limited sodium lauryl sulfate (disclosed in applicants claims 1-6 and 9-19 as the surfactant), polyvinylprrolidione (disclosed in applicants claims 1-6 and 9-19 as the water soluble polymer PVP), sodium citrate (disclosed in applicants claims 1-6 and 9-19 as the pH modifying agent), and calcium carbonate (disclosed in applicants claims 1-6 and 9-19 as an antioxidant), see page 3-4, column two, paragraph forty-eight in its entirety. The carrier can be a solvent or dispersion medium containing, for example, water, ethanol, propylene glycol, and polyethylene glycol, and suitable mixtures thereof (disclosed in applicants claims 10, 12, 15, 17 as aqueous and alcoholic solutions, ethanol in particular), see page four, column one, paragraph 51, lines 9-12.

Thus, Zhu et. al. teaches a composition for oral administration comprising a granulation of CCI-779 (the structure shown on page one, paragraph 8 wherein R^1 is –

$CO(CR^3R^4)_b(CR^5R^6)_dCR^7R^8R^9$; b=0, d=1, R^5 and R^6 are each $-(CR^3R^4)_fOR^{10}$, wherein R^3, R^4 R^{10}, and R are each hydrogen and f=2), a water soluble polymer (PVP), a surfactant (sodium lauryl sulfate), an antioxidant (calcium carbonate), and a pH modifying agent (sodium citrate).

In regards to claims 10-12 and 15-17, "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985), see also MPEP § 2113.

***Claim Rejections* – 35 USC § 103**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the

subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 13-14 and 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Zhu el. al. (US 2002/0055518 A1) as applied to claims 1-6 and 9-19 in view of Rubino et. al. (US 2004/0167152 A1), and in further view of Madhavi et. al. (Food Antioxidants: Technological, Toxicological, and Health Perspectives, Decker, 1996).

Zhu et al. teachings are as applied above for claims 1-6, 9-12 and 15-17.

Zhu et al. does not teach a composition of claim 12, wherein the antioxidant is butylated hydroxyanisole (BHA) and butylated hydroxytoluene (BHT).

Rubino et. al. teaches a formulation containing CCI-779, composed of CCI-779, an antioxidant, a diluent solvent, and a surfactant (see page 2, column 1, paragraph 16

in its entirety, for example). Acceptable antioxidants include, but are not limited to, citric acid, d,l-α-tocopherol, BHA, BHT (BHA and BHT are disclosed in applicant's claims 10 and 15), ascorbic acid, propyl gallate, and mixtures thereof (see page two, column one, paragraph eighteen, lines 3-6).

Madhavi et. al. teaches that BHA is perhaps the most extensively used antioxidant in food industry (see page 277, section 5.2.2, first paragraph, lines 1-2, for example). The absorption and metabolism of BHA has been studied in rats, rabbits, dogs, monkeys, and humans. BHA was rapidly absorbed from the gastrointestinal tract in rats, rabbits, dogs, and humans, rapidly metabolized and completely excreted (see page 278, toxicological studies, lines 1-4, for example). BHT is another antioxidant used extensively in the food industry and is widely used in combination with other antioxidants such as BHA, propyl galate, and citric acid (antioxidants disclosed on page 4 of the applicants specification as acceptable antioxidants), see page 283, paragraph three, butylated hydroxytoluene, lines 1-4, for example.

Accordingly, one having ordinary skill in the art at the time the invention was made would have found it obvious to formulate an oral composition comprising combination of Zhu et al. composition with the antioxidants BHA and BHT, since Rubino et. al. demonstrated a composition comprising the applicant's active compound (CCI-779) with BHA and BHT (see page 2, column 1, paragraph 16 in its entirety, and page two, column one, paragraph eighteen, lines 3-6).

The motivation for combining the composition of Zhu et. al. with comprising the antioxidants BHA and BHT is because the composition comprising CCI-779, BHA, and BHT has been demonstrated by Rubino et. al. Additionally, as taught by Madhavi et. al., BHA and BHT are extensively used antioxidants that are rapidly absorbed from the gastrointestinal tract, metabolized and completely excreted in humans (see page 277, section 5.2.2, first paragraph, lines 1-2, and page 283, paragraph three, butylated hydroxytoluene, lines 1-4, for example). Thus, a further motivation to combine the composition of Zhu et. al. comprising specifically the antioxidants BHA and BHT is because both antioxidants are commonly used and exhibit excellent absorption, metabolism and excretion in mammals (humans, rats, dogs, and rabbits), as taught by Madhavi et. al., which is a desired effect for oral formulations.

In regards to claims13-14, which is dependent on claim 10, and 18-19, which is dependent on claim 15: "Even though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process." In re Thorpe, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985), see also MPEP § 2113.

For these reasons the claimed subject matter is deemed to fail to patentably distinguish over the state of the art as represented by the cited reference. The claims 13-14 and 18-19 are therefore properly rejected under 35 USC § 103.

Conclusion

As a result of the above rejections, none of the claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kendra D. Carter whose telephone number is (571) 272-9034. The examiner can normally be reached on 8:30 am - 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

SREENI PADMANABHAN
SUPERVISORY PATENT EXAMINER